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ORIGINAL ARTICLE

Changes in gut microbial flora after Roux-en-Y gastric bypass and sleeve gastrectomy and their effects on post-operative weight loss

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Abstract

Bariatric surgery affects gut microbial flora due to the anatomical and physiological changes it causes in the gastrointestinal tract. Understanding the interaction between the gut flora, the type of bariatric surgery and weight loss may help improve bariatric surgery outcomes. This study was designed to compare the effects of Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG) on two main phyla of the gut microbiota in humans and evaluate their potential effect on weight changes. Thirty morbidly obese patients were divided into two groups and underwent laparoscopic SG or laparoscopic RYGB. The patients' weight changes and fecal samples were evaluated at baseline and 6 months after the surgery. A microbial flora count was carried out of the phyla *Bacteroidetes* and *Firmicutes* and *Bacteroides Fragilis*. Changes in the abundance of the flora and their correlation with weight loss were analyzed. After 6 months, the patients with a history of RYGB showed a significant decrease in stool *Bacteroidetes* while the reduction in the SG group was insignificant. *Firmicutes* abundance was almost unchanged following SG and RYGB. There was no significant change in *Bacteroides Fragilis* abundance in either of the two groups, but a positive correlation was observed between *Bacteroides Fragilis* and weight loss after SG and RYGB. Bariatric surgery can affect gut microbiota. It can be concluded that these changes are dependent on many factors and may play a role in weight loss.

Keywords Sleeve gastrectomy · Roux en Y gastric bypass · Microbial flora · Weight

Introduction

The number of obese and overweight people has doubled across the world since 1980. As of 2014, 52% of adults were overweight or obese, and morbid obesity is currently a public health problem [1]. Obesity increases the risk of life-threatening diseases, including type-2 diabetes, arterial hypertension, coronary heart disease, and cancer [2]. Although physical inactivity and inappropriate eating habits play a role in weight gain, studies suggest that genes are also responsible for obesity [3].

Obesity affects the intestinal microbiota, as well [4, 5]. The human gut hosts roughly 10^{14} microorganisms, which contain 2–20 million microbial genes [6]. Most human gut microbiota includes four major bacterial phyla: *Bacteroidetes* and *Firmicutes*, which collectively organize about 60% of the digestive tract bacteria [7], *Proteobacteria* and *Actinobacteria* [6]. In addition, *Bifidobacterium, Lactobacillus*, *Bacteroides*, *Clostridium, Escherichia* and *Streptococcus* are the most common gut bacteria in adults.

Gut microbial imbalance (dysbiosis) can be developed in a variety of ways, including dietary changes, stress, the host genetics, antibiotic consumption and contamination with pathogenic bacteria [8], or as a consequence of metabolic syndromes (such as obesity, type-2 diabetes, etc.),

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neurological diseases, allergies, Irritable Bowel Syndrome (IBS), and Inflammatory Bowel Disease (IBD) [9].

Bariatric surgery is reported to be the most successful treatment for morbid obesity and its related comorbidities. In general, bariatric surgery can prevent weight gain by different mechanisms [10]. Roux-en-Y gastric bypass (RYGB) is considered the gold standard in bariatric surgery as a restrictive-malabsorptive technique that results in excellent long-term weight loss and improvement in obesity-related comorbidities. The highest number of operations performed in the US pertains to Sleeve Gastrectomy (SG) [11] that has recently gained popularity because of its safety and simplicity, great results in terms of weight loss and a comorbidity improvement comparable to RYGB [12].

Postoperative changes in the gut microbiota are associated with improvement in metabolic state and remission of inflammatory responses after surgery [13], which suggests that alterations of the gut microbiota may be one of the mechanisms by which bariatric surgery improves metabolism and contributes to long-lasting body weight reduction and the resolution of obesity-related comorbidities.

In the literature, changes in gut microbiota following bariatric surgery have been evaluated, but controversial results are achieved [14–18]. Some studies have shown a decrease in the relative abundance of *Firmicutes* after SG and an increase in *Bacteroidetes* following RYGB [14]. Meanwhile, some other studies concluded RYGB leads to an increase in *Firmicutes* phyla, but a decrease in *Bacteroidetes* phyla, and that SG increased *Bacteroidetes* phyla [15]. However, some studies revealed no changes in *Firmicutes* and *Bacteroidetes* following bariatric surgery [16].

Given the controversial results of these studies, the present study compares the effects of RYGB and SG on two main phyla of the gut microbiota in humans and evaluates their potential effect on weight changes and examines whether postoperative gut microbiota are correlated with BMI changes.

Materials and methods

Thirty morbidly obese patients with BMI > 40 were studied from February to May 2019 after submitting their consent form. At first, demographic data, including age, gender, weight, height and BMI, were registered and all the patients gave fecal samples. Based on factors such as eating habits, presence and grade of hiatal hernia, comorbidities and GERD symptoms, the patients were divided into two groups who underwent either laparoscopic sleeve gastrectomy (LSG) or laparoscopic Roux-en-Y gastric bypass (LRYGB). The inclusion criteria for the RYGB group included snacking, medium or large hiatal hernia, type-2 diabetes, GERD symptoms and esophagitis grade B or above. The other individuals underwent SG.

The surgeries were performed by the same surgical team. LRYGB entailed the formation of a small gastric pouch approximately 6 cm in length and 36 French in diameter along the lesser curvature of the stomach, and the jejunum was then divided 125 cm distal to the ligament of Treitz. End-to-side gastrojejunostomy about 3 cm in diameter using a linear stapler was then carried out, followed by a side-to-side jejunojejunostomy 75 cm distal to the gastrojejunostomy. At last, jejunojejunostomy and Petersen's defects were closed. LSG included the gastrolysis of a greater curvature, continued by stapling the stomach from 4 cm by pylorus to the His angle beside a 36 French caliber tube. Omentopexy was also performed to prevent sleeve twisting. All the patients were discharged the next day after the surgery with a drug prescription containing Ursodeoxycholic Acid (UDCA), 300 mg, twice daily as prophylaxis for gallstone formation and Proton Pump Inhibitor (PPI), 40 mg, twice daily, for 6 months and multivitamins daily. The follow-up visits were performed on the 3rd and 10th days and 1st, 3rd and 6th months after surgery. In the postoperative period and follow up visits, no complication was detected. Furthermore, the patients refrained from using antibiotics or other items affecting the gut microbiota during this period.

After 6 months, they were re-examined, their weight was measured and fecal samples were taken. The stool specimens were transferred to special containers to add DNA and RNA stabilizers to them at the university's microbiology laboratory. The samples were stored at − 20 °C (cold chain was observed for transferring the samples). The samples were extracted using a fecal extraction kit according to the manufacturer's protocol and were stored in a freezer at − 80 °C for subsequent testing. The primers required for the microbial flora species, including *Bacteroidetes* phylum, *Firmicutes* phylum and *Bacteroides Fragilis,* were requested to be synthesized by the primer synthesis company and were kept at − 20 °C for further testing.

The experiments were performed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) at the microbiology department of the university and the results were recorded.

Statistical analysis

Data were presented as mean and standard deviation (SD) for the continuous variables and as percentages for the categorical variables. The Kolmogorov–Smirnov test was used before performing further analyses, and log transformation was used for the variables with a significant deviation from the normal distribution. A Chi-square (χ^2) test was used for comparing the categorical data between the two groups. A paired-sample *t* test or Wilcoxon's test was used to calculate the changes within the groups 6 months after surgery. Mann–Whitney's U test was used to calculate the differences and changes from the baseline between the groups for the continuous data. Spearman's correlation test was used to demonstrate correlations. All the statistical tests were performed in SPSS-17 (SPSS Inc., Chicago, IL, USA) with the 0.05 significance level.

Results

Thirty morbidly obese patients who were candidates for bariatric surgery were enrolled in this study. Twenty-three patients (76.7%) were female. The mean ± standard deviation (SD) of age was 37 ± 9.73 (range 18–62 years) and the mean ± SD of BMI was 44.61 ± 3.77 (range 38.21–51.20 kg/m^2). Eighteen (60%) of the patients underwent sleeve gastrectomy (SG group) and 12 (40%) Roux-en-Y gastric bypass (RYGB group). As shown in Table 1, the groups were similar at baseline in terms of characteristics such as age, gender, BMI, *Bacteroidetes* phylum, *Firmicutes* phylum and *Bacteroides Fragilis*. Table 1 presents the baseline characteristics of both groups.

Post-operative analysis

Six months after the surgery, the mean ± SD of excess weight loss (EWL%) was 57.72 ± 15.08%. The type of bariatric surgery ($P = 0.371$), gender ($P = 0.163$), and age ($P = 0.164$) had no significant effect on EWL.

Table 2 shows the changes in the measured characteristics at baseline and 6 months after the surgery between the SG and RYGB groups and within each group.

At this time, BMI reduced significantly in the SG and RYGB groups ($P < 0.001$ for both groups); the between-group analysis revealed that BMI reduction did not differ

Table 1 The baseline characteristics between the two different bariatric surgery groups

P value	RYGB ($N = 12$)	SG ($N = 18$)	Variables
1	37 ± 10.81	37 ± 9.27	Age, mean ± SD, years
0.669	10 (83.3%)	13 (72.2%)	Females, no. (percent)
0.560	122.62 ± 15.92	119.07 ± 16.26	Weight, mean ± SD, kg
0.188	45.73 ± 3.94	43.87 ± 3.56	BMI, mean ± SD, kg/m^2
0.961	9.62 ± 0.59	9.63 ± 0.6	*Bacteroidetes* phylum, mean ± SD
0.884	8.12 ± 0.69	8.05 ± 0.8	*Firmicutes* phylum, mean ± SD
0.950	0.03 (0.004, 0.1)	0.02 (0.01, 0.08)	*Firmicutes/Bacteroidetes* ratio, median (IQR)
0.091	5.25 ± 1.31	6.24 ± 1.77	*B Fragilis*, mean ± SD

SG Sleeve Gastrectomy, *RYBG* Roux-en-Y Bypass Gastrectomy, *BMI* Body Mass Index, *IQR* Inter Quartile Range, *SD* Standard Deviation

Table 2 The changes in the measured characteristics from baseline to 6 months after the surgery

Variables	SG group ($N = 18$)		RYGB group ($N = 12$)		Total ($N = 30$)	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
BMI, Mean ± SD, kg/m^2	43.87 ± 3.56	32.59 ± 3.29[§]	45.73 ± 3.94[a]	34.65 ± 4.71[a§]	44.61 ± 3.77	33.41 ± 3.98[§]
Weight, mean ± SD, kg	119.07 ± 16.26	88.82 ± 11.70[§]	122.62 ± 15.92[a]	93.28 ± 15.36[a§]	120.49 ± 15.94	90.60 ± 13.22[§]
EWL%, mean ± SD, kg	–	59.77 ± 13.47	–	54.65 ± 17.38[a]		57.72 ± 15.08
Bacteroidetes phylum, mean ± SD	9.63 ± 0.60	9.28 ± 0.58	9.62 ± 0.59[a]	8.76 ± 0.93*	9.62 ± 0.59	9.07 ± 0.77[§]
Firmicutes phylum, mean ± SD	8.05 ± 0.8	8.28 ± 0.82	8.12 ± 0.69[a]	7.83 ± 0.82	8.07 ± 0.74	8.10 ± 0.84
Firmicutes/Bacteroidetes ratio, median (IQR)	0.02 (0.01, 0.08)	0.09 (0.03, 0.32)	0.03 (0.01, 0.1)[a]	0.06 (0.03, 0.66)	0.03 (0.01, 0.08)	0.07 (0.03, 0.391)*
B Fragilis, mean ± SD	6.24 ± 1.77	6.86 ± 1.66	5.25 ± 1.31[a]	6.15 ± 2.60	5.84 ± 1.66	6.58 ± 2.08

BMI Body Mass Index, *EWL* Excess Weight Loss, *SG* Sleeve Gastrectomy, *RYBG* Roux-en-Y Bypass Gastrectomy, *IQR* Inter Quartile Range, *SD* Standard Deviation

[a]Compared with SG group, $P > 0.05$

*Compared with preoperative, P value < 0.05

[§]Compared with preoperative, P value < 0.01

significantly between the SG and RYGB groups ($P = 0.168$). The same result was obtained for weight reduction ($P = 0.765$) and EWL% ($P = 0.371$).

Firmicutes phylum, *Bacteroidetes* phylum, *Firmicutes/Bacteroidetes* ratio and *B Fragilis* 6 months after the surgery

As shown in Table 2, the patients who underwent RYGB had a significant reduction in their *Bacteroidetes* count compared to pre-surgery ($P = 0.024$), but this reduction was not significant in the SG group ($P = 0.071$), and changes in the *Firmicutes* count compared to pre-surgery were not significant in either the SG ($P = 0.329$) or RYGB ($P = 0.407$) groups.

The *Firmicutes* to *Bacteroidetes* ratio was not significantly different from the baseline in the SG ($P = 0.145$) or RYGB ($P = 0.06$) groups. Also, after surgery, this change was not significantly different between the two groups (Table 2, $P = 0.687$).

The *B Fragilis* count did not differ significantly between the baseline and 6 months post-surgery in the SG and RYGB groups or between the two groups ($P > 0.05$ for all). Without considering the type of bariatric surgery, the analysis revealed a significant overall reduction in the *Bacteroidetes* count ($P < 0.01$) and a significant increase in the *Firmicutes* to *Bacteroidetes* ratio (Table 2, $P = 0.037$).

The correlation between the *Bacteroidetes* and *Firmicutes* counts and the *Firmicutes/Bacteroidetes* ratio and *B Fragilis* count with age, BMI and EWL%

There were no significant correlations for the pre-operative *Bacteroidetes*, *Firmicutes*, *Firmicutes/Bacteroidetes* ratio and *B Fragilis* with age, pre-op BMI and EWL% ($P > 0.05$ for all; Table 3).

Six months after the surgery, a significant negative correlation was observed between the *B Fragilis* count and post-op BMI in the RYGB subgroup ($P = 0.035$; $r = -0.612$) and a significant positive correlation was observed between the *B Fragilis* count and EWL% in the SG group ($P = 0.028$; $r = 0.518$; Table 4).

Discussion

While bariatric surgery is the most effective treatment for morbid obesity, there is a lot remaining to understand about it. Previous studies have demonstrated alterations in gut

Table 3 Correlation of age, pre-op BMI and EWL% with pre-op count of *Bacteroidetes*, *Firmicutes*, *Firmicutes/Bacteroidetes* ratio and *B Fragilis*

Correlation with	Age Sig (r value)	Pre-op BMI Sig (r value)	EWL% Sig (r value)
Pre-op *Bacteroidetes*	0.202 ($r = -0.240$)	0.612 ($r = 0.097$)	0.147 ($r = 0.271$)
Pre-op *Firmicutes*	0.588 ($r = 0.103$)	0.378 ($r = -0.167$)	0.697 ($r = 0.074$)
Pre-op *Firmicutes/Bacteroidetes* ratio	0.149 ($r = 0.270$)	0.353 ($r = -0.176$)	0.457 ($r = -0.141$)
Pre-op *B Fragilis*	0.152 ($r = -0.268$)	0.283 ($r = -0.203$)	0.201 ($r = 0.240$)

Table 4 Correlation of age, post-op BMI, EWL% with post-op count of *Bacteroidetes*, *Firmicutes*, *Firmicutes / Bacteroidetes* ratio and *B Fragilis* in surgical subgroups

Correlation with	Age Sig (r value)	Post-op BMI Sig (r value)	EWL% Sig (r value)
Post-op *Bacteroidetes*			
SG group	0.354 ($r = 0.232$)	0.359 ($r = -0.320$)	0.288 ($r = 0.265$)
RYGB group	0.958 ($r = -0.017$)	0.100 ($r = 0.497$)	0.329 ($r = -0.308$)
Post-op *Firmicutes*			
SG group	0.293 ($r = 0.262$)	0.903 ($r = 0.031$)	0.647 ($r = -0.116$)
RYGB group	0.841 ($r = -0.065$)	0.158 ($r = 0.434$)	0.230 ($r = -0.375$)
Post-op *Firmicutes/Bacteroidetes* ratio			
SG group	0.671 ($r = 0.108$)	0.295 ($r = 0.261$)	0.138 ($r = -0.363$)
RYGB group	0.551 ($r = 0.192$)	0.863 ($r = -0.056$)	0.820 ($r = 0.074$)
Post-op *B Fragilis*			
SG group	0.131 ($r = -0.370$)	0.074 ($r = -0.431$)	0.028 ($r = 0.518$)
RYGB group	0.955 ($r = 0.018$)	0.035 ($r = -0.612$)	0.153 ($r = 0.439$)

microbiota associated with bariatric surgery and a relationship between altered microbiota and metabolic features; however, various mechanisms are at play in bariatric surgery outcomes that should be investigated [18].

The gut microbiota plays a critical role in human health in that bacteria produce enzymes for carbohydrate metabolism, short-chain fatty acids, lipopolysaccharides and secondary bile acids [5] which enter the circulatory system to influence inflammation, immunity, energy homeostasis, and intestinal transit regulation [7].

Changes in the gut microbiota have been shown to be correlated with some metabolic factors such as BMI, fat mass, calorie intake, satiety hormones and appetite [14]. Another study further demonstrated that altered gut microbiota after RYGB contribute to a reduction in the host's body weight and adiposity, and the transfer of post-RYGB gut microbiota to germ-free mice also resulted in lost body weight [19].

The gut microbiota composition has been shown to differ significantly between obese and lean people, with a higher ratio of *Firmicutes* to *Bacteroidetes* in the obese [20]. The gut microbiota of obese people has a lower bacterial variety compared to that in lean individuals [21].

One systematic review showed that the majority of studies have found a decrease in the abundance of *Firmicutes* and an increase in *Bacteroidetes* following bariatric surgery [14]. Nonetheless, one study revealed higher *Firmicutes* after both RYGB and SG in relation to the pre-operative levels [15]. Gastric bypass has also been shown to reduce *Bacteroidetes* and *Bacteroides* counts [16].

A clinical study revealed that SG can lead to obvious changes in the metabolic properties of obese patients, perhaps due to the shifts in gut microbiota [17]. Likewise, another study reported permanent changes in the composition of the gut microbiota after SG, including an increase in *Bacteroidetes* and a decline in *Firmicutes*. They also showed correlations between some bacterial families and metabolic improvements after SG [18]. According to these different results, this study was designed to compare the effects of RYGB and SG on two main phyla of the gut microbiota.

The present study examined 30 morbidly obese patients with a mean BMI of 44.61 kg/m^2 and a mean age of 37 years who underwent SG and RYGB. Following surgery, at the 6th month's post-operation visit, *Bacteroidetes* phylum, *Firmicutes* phylum and *Bacteroides Fragilis* counts were evaluated in the stool specimens. At baseline, the demographic data and microbiota phyla counts were not significantly different between the SG and RYGB groups.

Six months after surgery, the mean EWL% was $57.72 \pm 15.08\%$, independent of gender and age; also, there was no significant difference between the SG and RYGB groups in EWL%. The patients who had undergone RYGB encountered a decrease in stool Bacteroidetes after 6 months, which could have been caused by pH reduction after bariatric surgery. The same was reported in the study by Murphy et al. [15]. The present findings also showed a non-significant reduction in Bacteroidetes count in the SG group, which is in contrast with the findings reported by Davis et al. [14]. Medina et al. also revealed that Firmicutes abundance was almost unchanged following SG and RYGB, as consistent with the present study [22].

As previously reported, these changes may be due to diet, changes in acid exposure after different surgical procedures and the consumption of drugs such as PPIs [23]. Medina et al., however, found that various changes in microbiota lead to an increase in the *Bacteroides/Firmicutes* ratio in patients with a history of SG but a significant decrease in the RYGB group [22]. This finding is in contrast with the present study finding, as the patients in this study did not show any significant changes in the *Bacteroides/Firmicutes* ratio after surgery in either SG or RYGB groups.

According to the present findings, there was no significant change in *Bacteroides Fragilis* abundance between the pre-operation and post-operation stool samples. Meanwhile, Fernanda et al. detected a decrease in *Bacteroides* abundance in connection with increased serum bilirubin after SG and RYGB [24]. The data in the present study did not show any significant correlations for the pre-op microbiota phyla with age and pre-op BMI, and EWL% did not have a correlation with the gut microbiota count either; it can thus be concluded that the pre-op gut microbiota components do not have an effect on weight changes following bariatric surgery.

This study did not find any correlations for age, post-op BMI, and EWL% with the post-op count of *Bacteroidetes* and *Firmicutes* and the *Firmicutes/Bacteroidetes* ratio in the two groups, which demonstrates that weight changes after SG and RYGB are independent of post-operation *Firmicutes* and *Bacteroidetes* abundance, which is in line with the results of previous studies [22].

Six months after the surgery, a negative correlation was found between BMI and the *B Fragilis* count in the RYGB group and a positive correlation between the *B Fragilis* count and EWL% in the SG group, showing the potential effect of *B Fragilis* on weight loss. The present findings are in agreement with those reported by Santacruz A. et al., which demonstrated a positive correlation between *Bacteroides Fragilis* changes and weight loss after lifestyle modification by calorie intake restriction and increased exercise. These researchers also explained that *B Fragilis* changes are strongly dependent on diet, especially carbohydrate consumption [25]. This is related to the aim of designing this study; we did not find any evidence in the literature of the relationship of *B Fragilis* changes with weight loss following bariatric surgery.

There is an ongoing debate about these correlations because the cause and effect relationship between gut microbiota changes and weight changes is not clearly defined yet, although one study reported weight gain in a healthy human after fecal microbiota transplantation from another overweight human [26]. Likewise, some studies revealed that fecal microbiota transplantation (FMT) from lean healthy people can lead to weight loss in morbid obese patients [6, 27, 28].

It should be noted that gut microbiota changes are multifactorial, depending on geographic area, economic status, diet and calorie intake. According to the present findings, gut microbiota change patterns following bariatric surgery were in contrast with most of the previous studies, which can be a result of the differences in race and nutritional patterns. Stool sampling also demonstrates mostly large intestine microbe changes, and assessing the upper intestinal parts for microbe changes is difficult [22].

The most important limitations of this study were small sample size and basal characteristic differences in patients. Further evaluations should be carried out with a greater sample size to compare the groups according to race, diet and nutritional patterns. Other less-noticed bacterial species should also be examined in future studies.

Conclusion

To conclude, bariatric surgeries can affect gut microbiota and change it by unknown mechanisms. Previous studies have demonstrated various results and changes in gut microbiota after bariatric surgery. These changes which depend on many factors may have a role in weight loss. Based on the researchers' best knowledge, this study is the first report in humans that shows a positive correlation between *Bacteroides Fragilis* and weight loss after SG and RYGB; therefore, fecal microbiota transplantation in obese patients containing *B Fragilis* or probiotics consisting of *B Fragilis* bacteria may accelerate and amplify weight loss after bariatric surgical procedures. However, further studies should be performed to find more specific and effective microbiota for weight loss in morbid obese patients.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MK, MT, NM, AP and MP. The first draft of the manuscript was written by RK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions of their containing information that could compromise the privacy of research participants.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants The protocol of this study was approved by the ethics committee of Iran University of Medical Sciences with this number: IR.IUMS.REC 1395.95-02-140-27464.

Informed consent Informed consent to participate in the study was obtained from the participants.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication Informed consent for data publication was obtained from the participants in the study.

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